REMARKS

Applicant has resubmitted the Sequence Listing filed on December 22, 2009, to the address for the receipt of sequence listings as indicated by the Examiner on page 2 of the office communication.

Applicant acknowledges the withdrawal of the rejection of claims 6, 7, 9 and 10 under 35 USC 112, first paragraph, and the rejection of claims 2 and 3 as being obvious in view of Leong et al.

The rejection of claim 2 under 35 USC 103(a) as being unpatentable over Kashmiri et al (critical reviews in oncology/hemotology), 2001, Vol. 38 page 3-16 in IDS on 1/20/2010, in view of Leong et al (Cytokine, November 2001, Vol. 16, p. 106-119) is respectfully traversed.

Applicant has further amended claim 2 dividing paragraph (a) into three steps (a), (b) and (c) for purposes of clarity. Applicant, in step 2(a), uses aniline scanning mutatageous for the purpose of first replacing each i.e. all amino acid residue in the entire CDR of a murine monoclonal antibody. Step 2(b) follows which requires comparing antigen K_d values of residues substituted with aniline for selecting a transformant residue having a lower affinity to the human antigen K_d than of the original murine antibody.

Step 2(c) requires determining the replaced amino acid residue of the selected transformant as a specificity determining residue (SDR) and finally step 2(d), which must be carried out last, involves subsequently grafting the SDR to at least one of the corresponding amino acid residues into human antibody variable regions.

The Examiner acknowledges the sequential order of the steps in claim 2 which requires first performing alanine scanning mutagenenesis to determine a SDR and subsequently grafting the SDR to produce a humanized antibody. This results in minimizing a HAMA response which is indicated as a problem in a humanized antibody. However, the Examiner points out that since alanine scanning mutagenesis is a known technique which is disclosed in the cited reference Leong et al. (hereinafter "D1") and that the technique of selecting SDRs using a mutational analysis and grafting the selected SDRs into a human antibody is disclosed in Kashimiri et al (hereinafter "D3"), claim 2 is obvious. The Examiner further alleges that the experimental antibody in the present application has been disclosed in Maeng et al. (hereinafter "D2").

Leong et al, reference "D1", discloses a method of identifying high affinity binding residues in the CDR of a Fab fragment by performing alanine scanning mutagenesis on a Fab fragment of an already produced humanized antibody. The disclosure of Leong "D1" does not correspond to step (a) of claim 2 of the present application. Instead, step (a) of claim 2 of the present application performs alanine

scanning mutagenesis on the CDR of a murine monoclonal antibody, whereas D1 performs alanine scanning mutagenesis on the CDR of an already produced humanized antibody. As such, the subject antibodies are distinguishable from one another.

Furthermore, claim 2 of the present application also requires the step of ("2(b)") comparing antigen Kd values of residues substituted with alanine and the original residues for selecting a transformant residue having a lower affinity to the human antigen K_D than the original murine antibody and the step of ("2(c)") determining the replaced amino acid residue of the selected transformant as a specificity determining residue (SDR) before practicing step 2(d) which requires grafting the SDR to at least one of the corresponding amino acid residues into human antibody variable regions. Reference D1 selects high affinity binding residues by measuring the IC50 of wild type and variant mutants which is unrelated to the method of claim 2. Therefore, since Leong in D1 and step (a) of claim 2 have different subject antibodies for the performance of alanine scanning mutagenesis as well as different methods of selecting SDRs, Leong D1 does not make it obvious to perform alanine scanning mutagenesis on the CDR of a murine monoclonal antibody and does not make it obvious to perform step 2(b) in selecting SDRs.

Although alanine scanning mutagenesis is of itself a well known technique, performing alanine scanning mutagenesis on a murine monoclonal antibody for the purpose of selecting SDRs to be grafted into a human antibody as in claim 2 of the

present application is a novel concept totally different from that taught in reference D1.

Reference D3 (Kashimiri et al), which is a newly cited reference, is different from the present invention for the following reasons:

D3, (as is shown in Table 2) does not perform a mutational analysis that the murine antibody CC49 and human antibody LEN within the CDR have identical residues. Further, in Table 3, affinity is analyzed after residues, which are not identical, are mutated. In contrast, the present invention requires performing alanine scanning mutagenesis on each, i.e. on all amino acids within the entire CDR and their antigen-binding affinity must be compared with original antibodies in order to determine SDRs. This is not taught in D3 which uses a different method of selecting SDRs and does not perform a mutational analysis on all CDRs. Simply stated, reference D3 does not perform steps 4(a), 2(b) and 2(c) as recited in claim 2.

In the case wherein affinity is not analyzed after all CDRs are mutated, for example, middle chain ID nos. 33 and 35 in Table 2 can play an important role in binding to an antigen. D3, however, does not perform a mutation since the murine antibody and human antibody are the same residues (no. 33: Ala; no. 35: His) in D3. In such a case, it is difficult to achieve the effect of the present invention which is to minimize the area to be grafted by selecting optimal SDRs and grafting the selected SDRs, thereby resulting in the remarkable effect of inhibiting a HAMA response

(please refer to Example 9).

According to the method of the present invention and because of the last step of SDR grafting the amino acid sequences derived from non-self origin are minimized provided step 2(a) - step 2(c) is carried out prior to grafting in step 2(d).

Humanized antibodies produced by the method of the present invention are able to effectively reduce HAMA response. Substantially, the number of the peptide sequence in the humanized antibody of the present invention which binds to MHC class II was fewer than that of a humanized antibody produced by a conventional method (please refer to Example 9 in the present specification). In detail, as shown in tables 7 and 8, in the present invention there is (i) 48% reduction in heavy chain variable region, and (ii) 63% reduction in light chain variable region, compared to a conventional humanized antibody.

For all of the above reasons, claim 2 is clearly patentable over the cited references D1 and D3 taken individually or in combination and the rejection of claim 2 under 35 USC 103 should be withdrawn. Although the reference Maeng et al "D2" discloses the antibody KR127, it only selects a human antibody gene having the most similar sequence to the murine antibody KR127 which is produced as a humanized antibody, but does not disclose nor suggest a method of grafting the SDRs selected by a method of claim 3 of the present invention into a human antibody. Therefore, claim 3 of the present application is both distinct and inventive

in comparison to the prior art of D2 and is otherwise patentable for the reasons given above.

For all of the above reasons, claim 2 and dependent claims 3, 4, 5, 6, 7, 8, 9 and 10 are now believed to be in condition for allowance.

Reconsideration and allowance of claims 2-10 is respectfully solicited.

Respectfully submitted,

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CERTIFICATE OF TRANSMISSION

I hereby certify that this Amendment is being submitted to the U.S. Patent Office via EFS- Web to the Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450 on August 24, 2010.

By